Guidelines for Treatment of uncontrolled bleeding

Essay

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By

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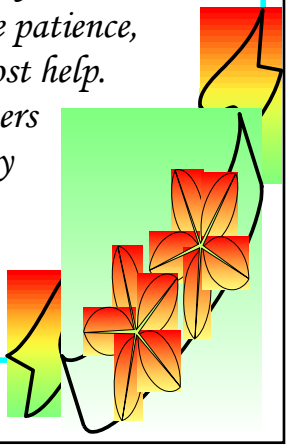

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List of Abbreviations

ACT	: Activated clotting time
ADP	: Adenosine di-phosphate
aPTT	: Activated partial thromboplastin time
AT3	: Antithrombin III
COX	: Cyclo-oxygenase
CPB	: Cardiopulmonary bypass
CRYO	: Cryoprecipitate
CT	: Closure time
DDAVP	: Desmopressin acetate, 1-desamino-8-D-arginine vasopressin
EACA	: Epsilon-aminocaproic acid
EDRF	: Endothelium-derived relaxing factor
FDA	: Food and Drug Administration
FDPs	: Fibrin degradation products
FFP	: Fresh frozen plasma
GPIa	: Glycoprotein Ia
GPIb	: Glycoprotein Ib
GPIIb-IIIa	: Glycoprotein IIb-IIIa complex
Hb	: Haemoglobin
Hct	: Hematocrit
HIT	: Heparin induced thrombocytopenia
IL-1	: Interleukin 1
INR	: International normalized ratio
KIU	: Kallikrein inactivator units
LMWH	: Low molecular weight heparin
NO	: Nitric oxide
NSAIDS	: Nonsteroidal anti-inflammatory drugs
PAI-1	: Plasminogen activator inhibitor-1
PFA-100	: Platelet function analyzer-100
PgI2	: Prostaglandin I2
PT	: Prothrombin time
PvO_2	: Mixed venous oxygen pressure
Q	: Cardiac output

List of Abbreviations (Cont.)

RBC	: Red blood cells
rFVIIa	: Recombinant activated factor VII
roTEG	: Rotational thromboelastography
SaO_2	: Arterial O_2 saturation
$ScvO_2$	: Central venous oxyhemoglobin saturation
Serpin	: Serine proteinase inhibitor
SLE	: Systemic lupus erythromatosis
TAFI	: Thrombin-activatable fibrinolysis inhibitor
TEG	: Thromboelastography
TF	: Tissue factor
TFPI	: Tissue factor pathway inhibitor
TNF	: Tumor necrosis factor
t-PA	: Tissue plasminogen activator
TT	: Thrombin time
TTD	: Transfusion-transmissible diseases
TxA2	: Thromboxane A2
u-PA	: Urokinase plasminogen activator
VO_2	: Oxygen uptake
vWF	: von Willebrand factor

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Introduction

Uncontrolled bleeding and coagulopathy are associated with trauma, liver failure, obstetric conditions, and a variety of surgical circumstances, resulting in increased morbidity and mortality in the critically ill (***Louise, 2007***).

Massive hemorrhage is often characterized by a surgical or vascular component and a coagulopathic component. The surgical/ vascular component can be corrected by surgical intervention or embolization. However, coagulopathic bleeding is more difficult to control.

Coagulopathy arises through several interrelated mechanisms, which include the consumption of coagulation factors and platelets through repeated attempts to form clots during massive hemorrhage, the dilution of coagulation factors as a result of fluid resuscitation, and metabolic disorders (hypothermia or acidosis), which can affect the coagulation process (***Spahn and Rossaint, 2005***).

Perioperative monitoring of blood coagulation is critical to better understand causes of hemorrhage, to guide hemostatic therapies, and to predict the risk of bleeding during the consecutive anesthetic or surgical procedures (***Ganter and Hofer , 2008***).

Treatment of coagulopathy requires a multidisciplinary approach. Blood products transfusion remains the cornerstone of management (***Vickie and Kim, 2008***) but Attempts to improve patient outcomes and minimize the use of blood and blood products have resulted in the investigation of alternative means of hemostasis (***Mohr et al., 2005***), and unlabeled adjunctive use of pharmacologic modalities that may reduce bleeding after major traumatic injuries (***Spahn et al., 2007***).

Aim of the work

The purpose of this essay research is to review the guidelines and strategies for management of uncontrolled bleeding.

Mechanisms of coagulation

Haemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system (***Kim et al., 2010***).

Haemostasis and clot formation require the interaction between a number of different procoagulant and anticoagulant mechanisms. The key elements required for haemostasis include: the blood vessel and its supporting structures; platelets and the platelet-vessel interaction; fibrin generation and regulation of the clot size by coagulation factor inhibitors and the fibrinolytic system.In a normal individual, there is a constant balance of procoagulant and anticoagulant activity to avoid pathological thrombosis or haemorrhage (***Vickie and Kim, 2008***).

I- Elements of haemostasis :

A) Endothelium and the vascular system :

Normal, intact endothelium does not initiate or support platelet adhesion and blood coagulation. Endothelial thrombo-resistance is caused by a number of antiplatelet and anticoagulant substances produced by the endothelial cells. Important vasodilators and inhibitors of platelet function are

prostacyclin (prostaglandin I2, PgI2) and nitric oxide (NO), formerly called endothelium-derived relaxing factor (EDRF). The thrombin-binding protein thrombomodulin and heparin-like glycosaminoglycans exert anticoagulant properties. Endothelial cells also synthesize and secrete tissue factor pathway inhibitor (TFPI), which is the inhibitor of the extrinsic pathway of blood coagulation. In addition, tissue plasminogen activator (t-PA) and its inhibitor plasminogen activator inhibitor-1 (PAI-1), which modulate fibrinolysis, are secreted by endothelial cells. Endothelial cells also possess some procoagulant properties by synthesizing and secreting Von Willebrand factor (VWF) and PAI-1. Following injury, these procoagulant factors and tissue factor (TF) activity are induced. This leads to adhesion and activation of platelets and local thrombin generation.

The hemostatic properties of the endothelial cells are modulated by cytokines such as endotoxin, interleukin (IL)-1, and tumor necrosis factor (TNF), resulting in an increased TF activity and down regulated thrombomodulin .

Small blood vessels comprise arterioles, capillaries, and venules. Only arterioles have muscular walls, which allow changes of the arteriolar caliber. Upon contraction, arterioles contribute to haemostasis, thus temporarily preventing extravasation of blood. Platelet secretion of thromboxane A2,

serotonin, and epinephrine promotes vasoconstriction during haemostasis .

B) Platelets :

Platelets are anuclear cells released from megakaryocytes in the bone marrow. Their life span in the peripheral blood is approximately 9 days. The average platelet count in peripheral blood ranges from 150,000 to 400,000 /μL. The formation of the initial platelet plug can be divided into separate steps, which are very closely interrelated in vivo: platelet adhesion, shape change, the release reaction, and platelet aggregation (***Reinhold et al., 2007*).**

1- Platelet adhesion :

Platelet adhesion to collagen is dependent on platelet membrane receptors: glycoprotein Ia (GPIa), which binds directly to collagen; and glycoprotein Ib (GPIb), which binds to Von Willebrand factor (vWF) in the plasma, and vWF in turn adheres to collagen.

2- Shape changes and release reactions :

Following adhesion, platelets undergo a shape change from a disc to a sphere, spread along the subendothelium and release the contents of their cytoplasmic granules, i.e. the dense bodies (containing ADP and serotonin) and the α-granules (containing platelet-derived growth factor, heparin

antagonist (platelet factor 4), β-thromboglobulin, fibrinogen, vWF, fibronectin, thrombospondin and other factors).

The release of Adenosine di-phosphate (ADP) leads to a conformational change in the fibrinogen receptor, the glycoprotein IIb-IIIa complex (GPIIb-IIIa), on the surfaces of adherent platelets allowing it to bind to fibrinogen .

3- Platelet aggregation :

Fibrinogen then binds platelets into activated aggregates (platelet aggregation) and further platelet release occurs. A self-perpetuating cycle of events is set up leading to formation of a platelet plug at the site of the injury (***Kumar and Clark, 2009***).

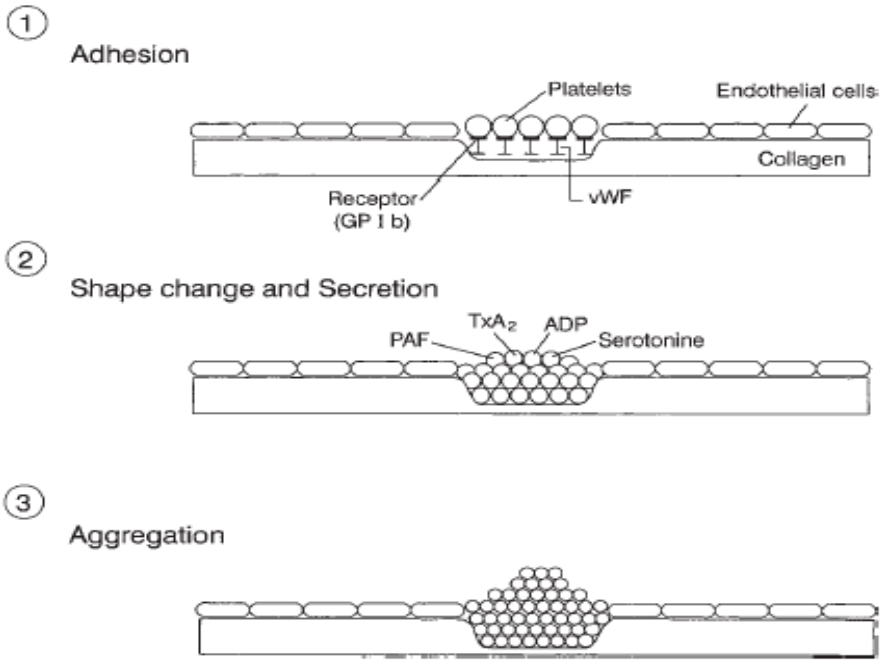

Fig 1. Platelet adhesion, shape change, secretion and aggregation (***Reinhold et al., 2007*).**

C) Coagulation factors, their inhibitors and fibrinolytic system:

1- Zymogens of serine proteases : Factor II,VII, IX, X (vitamin-K dependent factors), XI, XII.

2- Cofactors :Factor III (tissue factor), V, VIII.

3- Fibrinogen : Factor I.

4- Factor XIII.

5- Regulatory proteins: Protein C, S (vitamin-K dependent anti-coagulants), thrombomodulin and anti-thrombin III.